Myocardial Scar and Mortality in Severe Aortic Stenosis: Data from the BSCMR Valve Consortium

10.1161/CIRCULATIONAHA.117.032839

Myocardial Scar and Mortality in Severe Aortic Stenosis: Data from the BSCMR Valve Consortium

Running Title: *Musa et al.; Scar Predicts Mortality in Aortic Stenosis*

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Abstract

Background—Aortic valve replacement (AVR) for aortic stenosis (AS) is timed primarily on the development of symptoms; but late surgery can result in irreversible myocardial dysfunction and additional risk. This study aimed to determine whether presence of focal myocardial scar pre-operatively was associated with long-term mortality.

Methods—In a longitudinal observational outcome study, survival analysis was performed in patients with severe AS listed for valve intervention at six UK cardiothoracic centers. Patients underwent pre-procedure echocardiography (for valve severity assessment) and cardiovascular magnetic resonance for ventricular volumes, function and scar quantification between January 2003 and May 2015. Myocardial scar was categorized into three patterns (none, infarct or non-infarct patterns) and quantified using the full-width-at-half-maximum method as percentage of the left ventricle. All-cause and cardiovascular mortality were tracked for a minimum of 2 years.

Results—674 patients with severe AS (75±14years, 63% male; AV area 0.38±0.14cm^2/m^2; mean gradient 46±18mmHg, LVEF 61.0±16.7%) were included. Scar was present in 51% (18% infarct-pattern; 33% non-infarct). Management was surgical (SAVR, n=399) or transcatheter (TAVR, n=275). During follow-up (median 3.6 years), 145 (21.5%) died (52 post-SAVR, 93 post-TAVR). At multivariable analysis, the factors independently associated with all-cause mortality were age (HR 1.50, 95%CI: 1.11-2.04, p=0.009; scaled by epochs of 10 years), STS score (HR 1.12, 95%CI 1.03-1.22, p=0.007) and scar presence (HR 2.39, 95%CI 1.40-4.05, p=0.001). Scar independently predicted all-cause (26.4% vs 12.9%; p<0.001) and cardiovascular mortality (15.0% vs 4.8%; p<0.001), regardless of intervention (TAVR p=0.002, SAVR p=0.026 [all-cause mortality]). Every 1% increase in LV myocardial scar burden was associated with 11% higher all-cause mortality hazard (HR 1.11; 95%CI: 1.05-1.17; p<0.001) and 8% higher cardiovascular mortality hazard (HR 1.08; 95%CI: 1.01-1.17; p<0.001).

Conclusions—In patients with severe AS, late gadolinium enhancement on cardiovascular MR was independently associated with mortality; its presence being associated with a 2-fold higher late mortality.

Key Words: Aortic Stenosis; Scar; Mortality; Cardiovascular Magnetic Resonance

Clinical Perspective

What is new?

- In patients with severe aortic stenosis (AS), focal myocardial fibrosis (scar) determined by CMR was present in over 50% of patients and was associated with a 2-fold higher late mortality.
- Focal scar (both infarct and non-infarct patterns) was independently associated with all-cause and cardiovascular mortality after both surgical and transcatheter aortic valve replacement.

What are the clinical implications?

- In severe aortic stenosis, late gadolinium enhancement appears to be a useful biomarker of left ventricular remodeling, and its presence is associated with worse long-term outcomes following aortic valve intervention.
- This raises the hypothesis that for some patients, timing of aortic valve intervention may be too late once scar has developed, and that randomized trials of earlier intervention are now required.

Introduction

Aortic stenosis (AS) is the most common valvular heart disease.[1] It is characterized by progressive narrowing of the aortic valve and by hypertrophic remodeling of the left ventricular (LV) myocardium.[2] This process maintains wall stress and cardiac performance for many years but ultimately the LV decompensates, heralding the transition to heart failure, symptom development and death.[3] The treatment for AS is valve replacement, with the aim to reduce both symptoms and mortality.

Current guidelines recommend aortic valve intervention by surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) in symptomatic severe AS, or asymptomatic severe AS in the presence of LV dysfunction or exercise invoked symptoms.[4] However symptoms can be difficult to interpret, especially in the elderly who may be less active or have multiple co-morbidities, whilst reduction in ejection fraction is often irreversible and associated with increased risk of heart failure and death.[5]

Whilst the primary insult is the valve stenosis, the cardiac response to this may be equally important. Therefore, there is growing interest in objective and early markers of cardiac decompensation. Histological and imaging studies have suggested that focal myocardial fibrosis is a key driver in the transition from hypertrophy to heart failure.[6-10] Myocardial replacement fibrosis ("scar") can be detected by cardiovascular magnetic resonance (CMR) using the late gadolinium enhancement (LGE) technique. From single-center studies, focal fibrosis has been associated with increased levels of myocardial injury, diastolic and systolic dysfunction, EKG changes, and adverse clinical outcomes.[7-10] Focal scar by LGE is irreversible at 9 and 12 months post SAVR.[5, 11] CMR-detected myocardial fibrosis therefore appears to be a useful and objective biomarker of LV decompensation in aortic stenosis.

Prior studies have been too small to evaluate the independent association of imaging biomarkers and demographic factors with total and cardiovascular mortality in patients with severe AS.[7-10] We established a UK consortium to determine which pre-operative factors were most strongly associated with long-term post-operative mortality in patients with severe AS on conventional management pathways, which could potentially be used to time surgery better in the future. We hypothesized that myocardial scarring detected by LGE-CMR would be independently associated with mortality in patients with severe AS undergoing aortic valve intervention.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data are available from the corresponding author on reasonable request.

Patients and Study Design

A longitudinal, observational outcome study in patients with severe AS referred to six UK cardiothoracic surgical centers and listed for valve intervention (Brompton Hospital and Barts Heart Centre in London; Edinburgh Heart Centre; Glenfield Hospital in Leicester; Leeds Teaching Hospitals NHS Trust; John Radcliffe Hospital in Oxford). Between January 2003 and May 2015, patients were prospectively recruited after evaluation by the multi-disciplinary heart team. The study was approved by the UK National Research Ethics Service (13/NW/0832), conformed to the principles of the Helsinki Declaration, and all patients gave written informed consent. The primary endpoint was all-cause mortality. The secondary endpoint was cardiovascular disease-related mortality, as defined by diagnosis on the UK death certificate.

Inclusion criteria were patients >18 years with severe AS (one of: aortic valve area [AVA]<1cm^2, peak pressure gradient >64mmHg, mean pressure gradient >40mmHg, peak velocity >4m/s) who had undergone CMR imaging for research purposes.

Image Acquisition

Echocardiographic parameters were acquired as part of the clinical work-up following the guidelines for assessment of AS severity recommended by the American and European Societies of Echocardiography.[12] Global hemodynamic load was measured by calculating the valvulo-arterial impedance index (Zva), defined as the ratio of the estimated LV systolic pressure (sum of systolic arterial pressure and mean pressure gradient) to the stroke volume indexed for body surface area. CMR was performed on 1.5 Tesla (T) and 3T scanners using standardized protocols. In brief, cine images were acquired in long-axis planes and contiguous short-axis slices for ventricular volumes, mass and function. Phase-contrast velocity-encoded images were acquired for valve hemodynamics and the LGE technique was used to identify myocardial scar, as previously described.[13] All participating centers have previously published single-center mechanistic data in AS, where image quality and specific CMR pulse sequence parameters can be reviewed.[10, 14-17]

Data Management and Outcomes

Anonymized clinical and imaging (DICOM) data were collected and managed using REDCap (Research Electronic Data Capture) software[18] hosted at Barts Heart Centre/University College London. All deaths were identified through the UK National Health Service National Spine Database. Cardiovascular mortality was established in all deceased from the official death certificates, which in the UK list up to 3 causes of death, and were adjudicated by two readers (BP, JPG) blinded to all clinical data. Cardiovascular mortality was defined as death attributable

to myocardial ischemia and infarction, heart failure, cardiac arrest because of arrhythmia or unknown cause, or cerebrovascular accident.

Data Analysis

All CMR scans were centralized and re-reported in core-lab fashion by experienced readers blinded to clinical parameters using CVI42 software (Circle Calgary, Canada). Each center analyzed a single component of the CMR scan for the entire study population, according to a pre-specified standard operating procedure (*see supplement*), and after a period of training and reproducibility evaluation. LV volume and mass analysis was performed by manual contouring of the endo- and epicardial borders at end-diastole and end-systole.[19] Left atrial area and length at end-systole were measured in the horizontal (4-chamber) and vertical long axis (2-chamber) views for calculation of left atrial volumes by the biplane area length method and indexed.[19] Aortic flow for regurgitant volume and fraction was quantified from phase-contrast velocity-encoded images.[20] LGE was categorized by two observers into three patterns (none, infarct or non-infarct patterns) and quantified using the full-width-at-half-maximum method as percentage of the LV.[13] Examples of typical echocardiographic and CMR images can be seen in Figure 1. Further technical details of the image analysis can be found in the supplement.

Statistics

Statistical analysis was performed in R (version 3.0.1; The R Foundation for Statistical Computing). Distribution of data was assessed on histograms and using Shapiro-Wilk test. Continuous variables are expressed as mean ± 1 standard deviation or as median and interquartile range; categorical variables, as counts and percent. Baseline characteristics of participants were compared using the unpaired Student *t*-test, Mann-Whitney-Wilcoxon test, χ^2 or Fisher exact tests as appropriate. The primary endpoint was all-cause mortality. The secondary endpoint was

cardiovascular disease related mortality. Additionally, we computed early post-intervention (TAVR/SAVR) mortality (defined as 30-day or in-hospital mortality). Survival in patients with and without LGE was evaluated using the Kaplan-Meier method and compared among groups using the log-rank test. The index date was the date of CMR. Hazard ratios (HR) were expressed as mean ± 95% confidence intervals (CI).

All clinical parameters were proposed for inclusion in a univariate Cox proportional hazards model. The most predictive candidate variable was selected from each of three domains if applicable (clinical, echocardiography, CMR) to avoid co-linearity and then entered into the final model. Unique, clinically relevant predictor variables with a p value <0.10 in univariate analysis were entered into final multivariable models; a forward stepwise procedure was used. The incremental value between steps was measured by the χ^2 method. The proportional hazards assumption was tested with the use of log-log plots and examination of Schoenfeld residuals. All tests were 2 sided; $p<0.05$ was considered significant.

Role of the funding source

No additional funding was obtained for this consortium study beyond that of the original single-center research funding. Funders provided financial support for the original data collection, but had no role in the consortium study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the primary data and have final responsibility for publication.

Results

Baseline characteristics

Baseline characteristics of the 674 patients included are shown in Table 1 and Supplementary Figure S1 (Study Flow Chart). Mean age was (75±14 years, 63% male) with mean AVA 0.38±0.14 cm^2/m^2; mean gradient 46±18 mmHg. Median AV regurgitant fraction was 8.0% (IQR 2.7-17.3%); 16% of patients had at least moderately elevated pulmonary arterial systolic pressure (PASP, defined as 30-55mmHg by echocardiography). LV myocardial scar, as assessed by LGE, was present in 51% of patients, in a 2:1 ratio between non-infarct (33%) and infarct pattern scar (18%).

Management by surgical replacement versus transcatheter replacement

Management was SAVR (n=399) or TAVR (n=275). Median time from CMR to SAVR was 44 days (IQR 11–103 days), and to TAVR was 13 days (IQR 1–61 days). Compared to SAVR, patients managed with TAVR were older (79.2±7.8 vs 68.6±10.3 years, p<0.001), more likely female (48% vs 29%, p<0.001), with more atrial fibrillation (21.1% vs 6.5%, p<0.001) and more coronary artery disease (39.3% vs 19.5%, p<0.001), less hypertension (42.6% vs 59.5%, p<0.001) and fewer bicuspid aortic valves (5.5% vs 33.8%, p<0.001). TAVR patients had higher peak AV gradients and smaller AVA. Furthermore, TAVR patients had larger LV volumes, lower left ventricular ejection fraction (LVEF) and had more severe symptoms; LV mass and LGE prevalence were not different between groups, although infarct pattern scar was more prevalent in TAVR and non-infarct scar in SAVR groups.

Patient characteristics according to LGE status

LGE+ve patients were more likely to be male (72.7 vs 54.4%, p<0.001), to have had a previous myocardial infarct (17.0% vs 4.0%, p<0.001), had larger indexed LVEDV, higher indexed LV

mass, and lower LVEF (all p<0.001) than LGE-ve patients (Table 1). In the SAVR cohort only, males also had higher NYHA functional class (p=0.006) and higher systolic blood pressure (138.5±20.5 vs 134.0±17.8 mmHg, p=0.036).

Outcome

During a median 3.6 years follow-up (IQR 2.6-5.9 years), 145 (21.5%) patients died (52 post-SAVR and 93 post-TAVR). This equated to 52 deaths/1,000 patient years (27 and 104 for SAVR and TAVR groups, respectively). A cardiovascular cause of death was ascribed to 70 patients (10.4% of whole cohort; 19 post-SAVR [4.8%], 51 post-TAVR [18.5%]). 30-day post-intervention, overall mortality was 1.8% (n=12), with 1.3% (n=5) for SAVR and 2.5% (n=7) for TAVR, respectively; at 1-year, overall mortality was 6.2% (n=42), with 3.0% (n=12) for SAVR and 10.9% (n=30) for TAVR (Supplemental Table S1).

Predictors of Outcome

52 variables were compared to outcome (including demographic, comorbidities, therapies, STS score, and imaging [echocardiography/CMR] parameters). At univariate analysis (Tables 2, S2 and S3 for all, SAVR and TAVR, respectively), 28 of these were associated with outcome. At multivariable analysis (Tables 3, S4 and S5 for all, SAVR and TAVR, respectively), the factors independently associated with all-cause mortality were age (HR 1.50, 95%CI: 1.11-2.04, p=0.009; scaled by epochs of 10 years), STS score (HR 1.12, 95%CI 1.03-1.22, p=0.007) and scar presence (HR 2.39, 95%CI 1.40-4.05, p=0.001). The incremental effect of adding age, STS score and LGE presence to the risk stratification model is demonstrated in Figure S2; global Wald χ^2 are shown for separate Cox regression models predicting all-cause death. For cardiovascular mortality the factors independently associated with all-cause mortality were age (HR 1.94, 95%CI 1.44-2.60, p<0.0001; scaled by epochs of 10 years), female sex (HR 2.17,

95%CI 1.28-3.70, p<0.001), LGE presence (HR 3.14, 95%CI 1.65-5.99, <0.001), and reduced LVEF (HR 0.98, 95%CI 0.96-1.00, p=0.013). Pulmonary artery systolic pressure (PASP) was not included in the main model because data was only available in 63.3% (SAVR 82.7%, TAVR 49.5%), but when included, presence of severely elevated PASP (PASP>55mmHg) was an independent predictor of all-cause mortality (HR 2.73, 95%CI 1.21-6.17, p=0.016; Table S6). Neither coronary artery disease nor previous coronary revascularization (PCI or CABG) were independent predictors of mortality (Table S7). Furthermore, no echocardiographic or CMR markers of AV stenosis severity were independently predictive of mortality.

Patients with myocardial scar had higher (double) the all-cause (26.4% vs 12.9%; p<0.001) and three times the cardiovascular mortality (15.0% vs 4.8%; p<0.001). This was regardless of valve intervention type (TAVR p=0.002, SAVR p=0.026, Figure 2) and scar type, with both infarct and non-infarct scar being associated with similarly adverse outcomes (p<0.001 for both; see Figure 3) – example: all-cause mortality 25.2% non-infarct pattern LGE, 28.6% infarct pattern and 12.9% no LGE. Quantitatively, every 1% increase in LV myocardial scar burden was associated with 11% higher all-cause mortality hazard (HR 1.11; 95%CI: 1.05-1.17; p<0.001) and 8% higher cardiovascular mortality hazard (HR 1.08; 95%CI: 1.01-1.17; p<0.001, Table S8). There was no significant change in results when events within 30 days of intervention were excluded or the index date was changed from time of CMR to time of intervention (Table S9 and S10).

Discussion

In patients with severe AS, in terms of disease-based parameters, we have shown that myocardial fibrosis (scar) is independently associated with mortality. This was the case for all-cause and

cardiovascular mortality, after both surgical and transcatheter intervention, and for both infarct and non-infarct scar patterns. Specifically, every 1% increase in scar burden increased mortality hazard by 11% and cardiovascular mortality hazard by 8%. Given that most of this scar is AS related, and that scar was present in half of the patients, we postulate that for many patients, AS surgery is potentially occurring too late, and leaving patients with residual risk.

AS is important, being the most common valvular heart disease in the developed world (>3% of those over 75 years), and the advent of TAVR now offers a treatment option for many of those with significant co-morbidities who were previously deemed inoperable. Current guidelines recommend valve intervention to improve survival and symptom status when AS is severe and ventricular decompensation is present, suggested by the onset of symptoms or reduction in LVEF.[4] Importantly, we have highlighted in this study an additional component of this risk-benefit analysis that has been under-recognized: that is silent irreversible scar is very common and is associated with increased mortality. Moreover, the greater the scar burden, the higher the mortality. Previous studies have suggested that operating earlier may be beneficial for patients, but identifying which patients are likely to benefit is difficult given that many will remain asymptomatic for years. Our findings suggest that scar burden might be used to optimize the timing of surgical intervention, with half of patients demonstrating irreversible scar, and a consequent doubling of post-operative medium-term mortality. Non-infarct pattern scar was twice as prevalent as infarct scar, and both predicted worse outcome as previously suggested.[8, 9] In asymptomatic severe AS, the risks of early surgery (1-2% mortality) and prolonged risk of prosthesis-associated complications (e.g. endocarditis, pacemaker dependency, bleeding, thrombosis, valve degeneration) need to be balanced against the "silent" risk of sudden cardiac death (1.5%/year), and increased risk of intervention and long term outcome after symptoms

have developed.[21] Our results may therefore provide a mechanism for a better selection of appropriate patients for early surgery, but this remains to be tested.

Potential pathophysiology of scar formation

The ventricle in AS initially responds to pressure-loading by left ventricular hypertrophy resulting in adaptive LV remodeling to maintain wall stress and cardiac performance. Despite compensatory capillary vasodilatation, over time myocardial oxygen demand outstrips supply leading to subendocardial ischemia and eventually LV decompensation.[22-24] The transition to LV decompensation occurs by fibrosis and myocyte degeneration with irreversible cell loss, mainly by autophagy and oncosis.[6] This process is driven by subendocardial ischemia and preceded by two phenomena: perfusion defects and troponin elevation (indicating myocardial cell death).[25, 26] Replacement fibrosis ensues which starts in the subendocardial layers first and then over time affects deeper myocardial layers,[17] and in turn contributes significantly to the progression of LV systolic dysfunction.[6] Diffuse myocardial fibrosis, with increased collagen I and III deposition around cardiomyocytes and bundles, occurs predominantly in the mid-myocardium.[17] Patchy foci of fibrosis on LGE imaging can be indicative of widespread diffuse fibrosis. Diffuse fibrosis can be assessed by CMR T1 mapping,[17, 27] but was not investigated in this study, as it has only become available more recently.

Focal fibrosis identified by LGE is associated with adverse outcome across a wide range of myocardial pathologies,[28] and has been shown in small single center studies to be associated with outcome in AS.[7-10] The presented data place LGE-detected scar firmly as a key outcome predictor in AS and suggest that current timing of valve intervention (TAVR or SAVR), based on a combination of valve severity and symptoms, may be too late for optimal long-term outcomes. This was highlighted in a recently completed multi-center observational study in

asymptomatic patients with moderate-severe AS (PRIMID-AS; NCT01658345), the presence of scar on LGE did not predict symptom onset.[14]

Earlier intervention, for example in asymptomatic severe AS may therefore warrant investigation. Despite numerous observational studies to assess risk prediction in asymptomatic AS there have been no randomized trials of early intervention to improve outcome. Patients at risk of myocardial decompensation due to scar, or myocardium in the process of developing scar, can be identified early through the use of hs-Troponin, perfusion defects or CMR LGE techniques.[15] One study that will go some way to address this issue is EVOLVED-AS (NCT03094143), a parallel-group, multicenter, prospective randomized trial (open-label blinded endpoint) of early aortic valve intervention in asymptomatic patients with severe AS and evidence of LV decompensation, as evidenced by non-infarct pattern LGE. In the absence of prospective randomized trials, only registry data suggest the likely impact of early surgery.[29, 30]

Stratifying intervention based on the presence of LGE may be too late, since even the small amount of scar detected in our cohort, is associated with residual increased risk of all-cause and cardiovascular mortality, but until EVOLVED-AS and further studies report, the role, timing and intervals for CMR to guide decision making in patients with moderate-to-severe AS remain unclear.

Our study has limitations. This was an observational study of patients at surgical centers with an interest in CMR and echocardiography for clinical and research indications, potentially introducing selection bias. Due to the contra-indications for contrast enhanced CMR, patients with severe renal impairment and pre-operative pacemaker/defibrillators were not represented. Sixty-one patients did not undergo LGE imaging. There were no reported invasive measures of hemodynamics (during angiography), hematocrit, brain natriuretic peptides or blood troponin; as

per clinical routine renal function was checked prior to LGE CMR, but was not systematically captured or easily retrieved for this analysis. Furthermore, no routine imaging follow-up was performed. Although studies of other populations have shown that unrecognized infarct scar increases with age,[31] and can be found in up to 10% of subjects, this would only account for minority of the scar burden found in our population. Both TAVR and SAVR have been associated with de-novo LGE, which may be associated with further myocardial decompensation.[32, 33] Due to the lack of follow-up CMR data, the possibility of further peri-procedural damage could not be excluded. Finally, multivariate analysis was not controlled for the type of intervention, in particular this may have been important in TAVR where the learning curve and patient selection has changed over the years.

Conclusion

In patients with severe AS, pre-operative focal myocardial scar is independently associated with mortality; its presence being associated with a 2-fold higher late mortality.

Sources of Funding

This study was in part supported by the British Heart Foundation (University of Leeds, Greenwood JP [PG/11/126/29321]; University of Leicester, McCann GP [PG/07/068/2334]; University of Oxford, Myerson SG [FS/10/015/28104]; University of Edinburgh, Dweck MR [FS/10/026]; University College London, Moon JC [FS/08/028/24767]), the National Institute for Health Research (University College London, Treibel TA [DRF-2013-06-102]), including via its Biomedical Research Centre and Clinical Research Facility programmes, as well as Rosetrees Trust. The views expressed are those of the author(s) and not necessarily those of the UK National Health Service, National Institute for Health Research or Department of Health.

Contributors

JPG was the principal investigator of this study. MD, JCM, SGM, GPM, SP were co-investigators at each site. TAT wrote the manuscript. GC performed the statistical analysis. GC and GL provided statistical oversight. JPG, TAM and PB obtained ethics and co-ordinated the study. BP and JPG adjudicated the outcomes. GC set up and maintained the REDCap database. TAM, TAT, VV, AS, CC, RM performed the data collection, anonymisation and upload. TAM, JF and LD performed the CMR LGE analysis. VV and TM performed the atrial volume analysis. AS and JF performed the aortic flow analysis. TAT, CC, SP, ML, RM performed the left and right ventricular volume and function analysis. All authors have read and approved the manuscript.

Disclosures

None.

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Table 1. Baseline Characteristics

Variable	All Patients* (n=674)	+LGE (n=341)‡	–LGE (n=272)‡	*p*-value
Age, years	74.6 | 14.4	74.3 | 14.6	75.0 | 14.5	0.44
Intervention SAVR†	399 (59.2)	194 (56.9)	176 (64.7)	0.05
TAVR	275 (40.8)	147 (43.1)	96 (35.3)	
Male, No. (%)	425 (63)	248 (72.7)	148 (54.4)	**<0.001**
BMI, Kg/m^2	27.6 ± 5.1	27.8 ± 5.1	27.3 ± 4.8	0.20
Atrial Fibrillation, No. (%)	84 (12.5)	49 (14.4)	28 (10.3)	0.13
Diabetes Mellitus, No. (%)	146 (21.7)	77 (22.6)	58 (21.3)	0.71
Hypertension, No. (%)	358 (53.1)	184 (54.0)	155 (57.0)	0.46
Systolic BP, mmHg	135.0 ± 20.4	133.4 ±20.3	137.3 ± 20.2	**0.03**
Diastolic BP, mmHg	72.7 ± 12.2	72.2 ± 11.8	74.0 ± 11.8	0.10
Bicuspid Aortic Valve, No. (%)§	149 (22.1)	80 (23.5)	53 (19.4)	0.23
Known CAD, No. (%)	197 (29.2)	123 (36.1)	74 (27.2)	0.16
No previous PCI/CABG, No. (%)§	533 (79.1)	260 (76.2)	220 (80.9)	0.65
Previous PCI, No. (%)	57 (8.5)	38 (11.1)	16 (5.9)	0.07
Previous CABG, No. (%)	58 (8.6)	31 (9.1)	22 (8.1)	0.92
History of MI, No. (%)§	73 (10.8)	58 (17.0)	11 (4.0)	**<0.001**
STS Mortality Risk score, %	1.75 | 1.89	1.74 | 1.79	1.76 | 1.69	0.78
EuroSCORE II, %	1.81 | 2.4	1.87 | 2.85	1.64 | 1.69	0.07
NYHA Functional Class, No. (%)§				
I	81 (12.0)	33 (9.7)	47 (17.3)	**0.03**
II	258 (38.3)	138 (40.5)	90 (33.1)	
III	248 (36.8)	127 (37.2)	98 (36.0)	
IV	22 (3.3)	10 (2.9)	8 (2.9)	
Baseline Medications, No. (%)§				
ACE inhibitor or ARB	262 (38.9)	139 (40.8)	107 (39.3)	0.56
β-blocker	240 (35.6)	130 (38.1)	92 (33.8)	0.27
Aldosterone Antagonist*	36 (5.3)	21 (61.6)	11 (4.0)	0.12
Statin	406 (60.2)	224 (65.7)	162 (59.6)	0.23
Echocardiographic data				
Mean aortic valve gradient, mmHg	46.0 | 18.0	46.0 | 19.0	46.0 | 17.0	0.20
Peak aortic valve gradient, mmHg	78.0 | 30.0	78.0 | 30.0	79.5 | 30.0	0.34
AVA, cm^2	0.70 | 0.31	0.70 | 0.21	0.70 | 0.17	0.98
Indexed AVA [to BSA], cm^2/m^2	0.38 | 0.14	0.41 | 0.13	0.40 | 0.13	0.94
Estimated PASP, No. (%)§ Normal	316 (46.9)	159 (46.6)	138 (50.7)	0.85
Moderate (31-55mmHg)	80 (11.9)	43 (12.6	30 (11.0)	
Severe (>55mmHg)	30 (4.5)	16 (4.7)	11 (4.0)	
CMR data				

LV end diastolic volume index, mL/m^2	79.5 | 29.3	85.4 | 33.4	73.3 | 23.1	**<0.001**
LV stroke volume index, mL/m^2	46.2 | 14.5	46.0 | 14.9	45.8 | 14.2	0.80
LV Ejection Fraction, %	61.0 | 16.7	58.0 | 21.0	64.0 | 12.0	**<0.001**
Maximal LV wall thickness, mm	14.0 | 4.0	14.0 | 4.0	13.0 | 3.0	**<0.001**
LV mass index, g/m^2	81.0 | 31.0	87.1 | 31.3	74.9 | 28.5	**<0.001**
RV end diastolic volume index, mL/m^2	67.4 | 22.2	68.5 | 22.5	66.8 | 19.8	**0.015**
RV ejection fraction, %	65.0 | 13.0	63.8 | 15.0	65.0 | 11.0	**0.026**
Indexed left atrial volume, mL/m^2	52.8 | 25.7	53.3 | 24.4	51.4 | 25.4	0.19
CMR AoV regurgitant fraction, %	8.0 | 14.7	8.9 | 16.2	7.7 | 12.2	0.12
Valvulo-Arterial Impedance	3.93 | 1.4	3.93 | 1.3	3.98 | 1.5	0.20
LGE present, No. (%)	341 (50.6)	341 (100)	0	/
Non-infarct-pattern, No. (%)	222 (32.9)	222 (65.1)	0	/
Infarct-pattern, No. (%)	119 (17.7)	119 (34.9)	0	/
LGE mass, %	0.53‖ | 3.08	2.72 | 3.95	0	/

Normally distributed continuous variables are expressed as mean ± standard deviation; nonparametric continuous variables are expresssed as median | interquartile range; categorical variables are expressed as counts (percent).

* refers to all patient groups: all SAVR + TAVR; † refers to all SAVR: i.e. SAVR+SAVR/CABG

‡ For the LGE columns 61 subjects (32 TAVR and 29 SAVR) did not undergo late gadolinium enhancement imaging.

§ denotes that this variable of counts contains missing data, e.g. 46 missing in NYHA (incomplete data); 5 missing bicuspid AV data points; 26 baseline CAD missing data points; 1 missing MI data point.

‖ LGE mass (in %) as the median of all patients including those without LGE.

Abbreviations: ARB, angiotensin receptor blocker; AVA, aortic valve area; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LGE, late gadolinium enhancement; LV, left ventricle; MI, myocardial infarction; No., numbers; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; RV, right ventricle; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Table 2. Univariate Parameters

Parameter	ALL PATIENTS (n=674)				ALL PATIENTS (n=674)			
	All Cause Mortality (n=145)				Cardiovascular Mortality (n=70)			
	HR	Z	P value	95% CI	HR	Z	P value	95% CI
Baseline Demographics								
Age*	1.92	7.04	**<0.0001**	1.60 – 2.31	2.24	5.75	**<0.0001**	1.70 – 2.95
Male Sex	0.77	-1.58	0.115	0.55 - 1.07	0.55	-2.47	**0.014**	0.35 - 0.88
BMI	0.98	-1.40	0.161	0.94 - 1.01	0.97	-1.21	0.227	0.92 - 1.02
Atrial Fibrillation	2.33	4.202	**<0.001**	1.57 – 3.45	3.37	4.57	**<0.0001**	2.01 – 5.67
Diabetes Mellitus	1.32	1.48	0.139	0.91 - 1.90	1.93	2.63	**0.009**	1.18 – 3.14
Hypertension	1.06	0.37	0.715	0.77 - 1.47	1.02	0.08	0.940	0.64 - 1.63
Bicuspid AoV	0.28	-4.43	**<0.0001**	0.16 - 0.50	0.25	-3.23	**0.001**	0.11 - 0.58
Previous CAD	1.69	3.02	**0.003**	1.20 - 2.38	1.98	2.77	**0.006**	1.22 – 3.20
Previous PCI or CABG	1.51	2.09	**0.037**	1.03 - 2.24	1.82	2.17	**0.030**	1.06 – 3.11
Previous MI	0.74	-1.17	0.244	0.44 - 1.23	0.67	-1.10	0.271	0.33 -1.36
Baseline NYHA Functional Class								
II	2.70	2.12	**0.034**	1.08 - 6.80	2.82	1.39	0.163	0.66 – 12.17
III	4.16	3.05	**0.002**	1.66 – 10.40	5.60	2.35	**0.019**	1.33 – 23.52
IV	8.75	4.01	**<0.0001**	3.03 – 25.21	15.28	3.40	**<0.001**	3.17 – 73.67
Baseline Medications								
ACE inhibitor or ARB	1.37	1.78	0.076	0.97 - 1.94	1.50	1.61	0.107	0.92 - 2.44
β-blocker	1.19	1.04	0.300	0.85 - 1.67	1.45	1.53	0.127	0.90 - 2.32
Aldosterone Antagonist	0.82	-0.52	0.607	0.38 – 1.76	1.44	0.85	0.398	0.62 – 3.34
Statin	1.16	0.83	0.408	0.82 - 1.65	1.30	1.01	0.314	0.78 – 2.15
STS score	1.18	7.78	**<0.0001**	1.13 - 1.23	1.22	7.15	**<0.0001**	1.15 - 1.28
Euroscore	1.10	5.20	**<0.0001**	1.06 - 1.13	1.12	5.35	**<0.0001**	1.08 - 1.17
Echo Data								
Mean AoV gradient	1.00	0.84	0.402	0.99 – 1.02	0.99	-0.66	0.509	0.97 - 1.01
Peak AoV gradient	1.00	0.83	0.407	1.00 - 1.01	1.00	-0.33	0.740	0.99 - 1.01
AoV area	0.33	-2.30	**0.021**	0.13 - 0.85	0.23	-2.05	**0.040**	0.06 - 0.94
AoV area Indexed to BSA	0.30	-1.36	0.173	0.05 - 1.70	0.26	-1.03	0.301	0.02 – 3.32
Estimated PA pressure								
Moderate	2.10	2.73	**0.006**	1.23 - 3.58	3.07	2.86	**0.004**	1.42 - 6.63

Severe	4.09	3.98	**<0.0001**	2.04 – 8.20	7.10	4.28	**<0.0001**	2.90 - 17.41
CMR data								
LV end diastolic volume index	1.00	1.17	0.242	1.00 - 1.01	1.00	0.91	0.366	1.00 - 1.01
Indexed LV Stroke Volume	0.97	-4.27	**<0.0001**	0.95 - 0.98	0.96	-4.11	**<0.0001**	0.94 - 0.98
LV Ejection Fraction	0.98	-4.87	**<0.0001**	0.97 - 0.99	0.97	-5.06	**<0.0001**	0.95 - 0.98
Maximal LV wall thickness	0.93	-2.45	**0.014**	0.88 - 0.99	0.91	-2.22	**0.026**	0.84 - 0.99
Indexed LV mass	1.00	-0.29	0.769	0.99 - 1.01	1.00	-0.24	0.811	0.99 - 1.01
RV end diastolic volume index	1.00	-0.48	0.628	0.99 - 1.01	1.00	-0.15	0.878	0.98 - 1.01
RV Ejection Fraction	0.98	-3.29	**0.001**	0.96 - 0.99	0.96	-3.68	**0.002**	0.95 - 0.98
Indexed LA volume	1.01	3.17	**0.002**	1.00 - 1.02	1.02	3.66	**<0.001**	1.01 - 1.03
CMR AoV regurgitant fraction	0.99	-0.82	0.412	0.98 - 1.01	0.98	-1.32	0.186	0.96 - 1.01
Valvulo-Arterial Impedance	1.17	1.93	0.054	1.00 - 1.37	1.21	1.62	0.106	0.96- 1.51
Late gadolinium enhacement (LGE)								
LGE presence / absence	2.22	4.00	**<0.0001**	1.50 - 3.28	3.38	3.92	**<0.0001**	1.84 – 6.22
LGE pattern								
Non-infarct	2.08	3.40	**<0.001**	1.36 - 3.17	2.80	3.06	**0.002**	1.45 – 5.40
Infarct	2.49	3.79	**<0.001**	1.55 - 4.00	4.54	4.36	**<0.0001**	2.30 – 8.97
LGE mass, per 1% increase	1.07	4.00	**<0.0001**	1.04 - 1.11	1.09	3.78	**<0.001**	1.04 - 1.13

*Using age variable scaled by epochs of 10.

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; ARB, angiotensin receptor blocker; AVA, aortic valve area; PASP, pulmonary artery systolic pressure, LV, left ventricle; RV, right ventricle; LGE, late gadolinium enhancement.

Table 3. Multi-Variable Model – All Cause and Cardiovascular Mortality

	ALL PATIENTS (n=674)				
	ALL CAUSE MORTALITY (n= 145)				
Parameter	**HR**	**Z**	**P value**	**95% CI**	**Chisq (P value)**
CMR RV ejection fraction	1.01	0.89	0.374	0.99 – 1.04	–862.7 /
CMR LV ejection fraction	1.00	–0.15	0.879	0.98 – 1.02	12.5 (<**0.001**)
CMR BSA-Indexed LA Volume	1.00	0.64	0.520	0.99 – 1.02	140.4 (<**0.0001**)
Atrial fibrillation	1.39	0.87	0.383	0.66 – 2.92	7.3 (**0.007**)
LV maximal wall thickness	0.93	–1.85	0.064	0.85 – 1.01	4.6 (**0.032**)
STS Score	1.12	2.68	**0.007**	1.03 – 1.22	38.8 (<**0.0001**)
CMR BSA-Indexed LV SV	1.00	–0.21	0.832	0.97 – 1.02	3.9 (**0.050**)
CAD	0.99	–0.05	0.963	0.59 – 1.65	11.3 (<**0.001**)
AVA (by echo)	1.10	0.18	0.855	0.39 – 3.12	571.6 (<**0.0001**)
Age*	1.50	2.61	**0.009**	1.11 – 2.04	5.0 (**0.026**)
LGE Presence	2.39	3.22	**0.001**	1.40 – 4.05	129.7 (<**0.0001**)
Bicuspid AV	0.67	–1.01	0.315	0.31 – 1.46	1.95 (0.163)
	ALL PATIENTS (n=674) CV ONLY MORTALITY (n= 70)				
Parameter	**HR**	**Z**	**P value**	**95% CI**	**Chisq (P value)**
Female Sex	2.17	–2.89	**0.004**	1.28 – 3.70	-89.4 /
Previous CAD	1.53	1.60	0.110	0.91 – 2.56	28.0 (<**0.0001**)
CMR LV EF	0.98	–2.50	**0.013**	0.97 – 1.00	22.8 (<**0.0001**)
Atrial Fibrillation	1.43	1.17	0.240	0.79 – 2.58	8.2 (**0.004**)
Age*	1.94	4.41	<**0.0001**	1.44 - 2.60	21.3 (<**0.0001**)
LGE Presence	3.14	3.47	<**0.001**	1.65 – 5.99	82.2 (<**0.0001**)

*Using age variable scaled by epochs of 10.

Abbreviations: AVA, aortic valve area; BSA, body surface area, CAD, coronary artery disease; LA, left atrium, LGE, late gadolinium enhancement; LV, left ventricle, SV, stroke volume.

Figure Legends

Figure 1. Multi-modality Assessment of Aortic Stenosis.

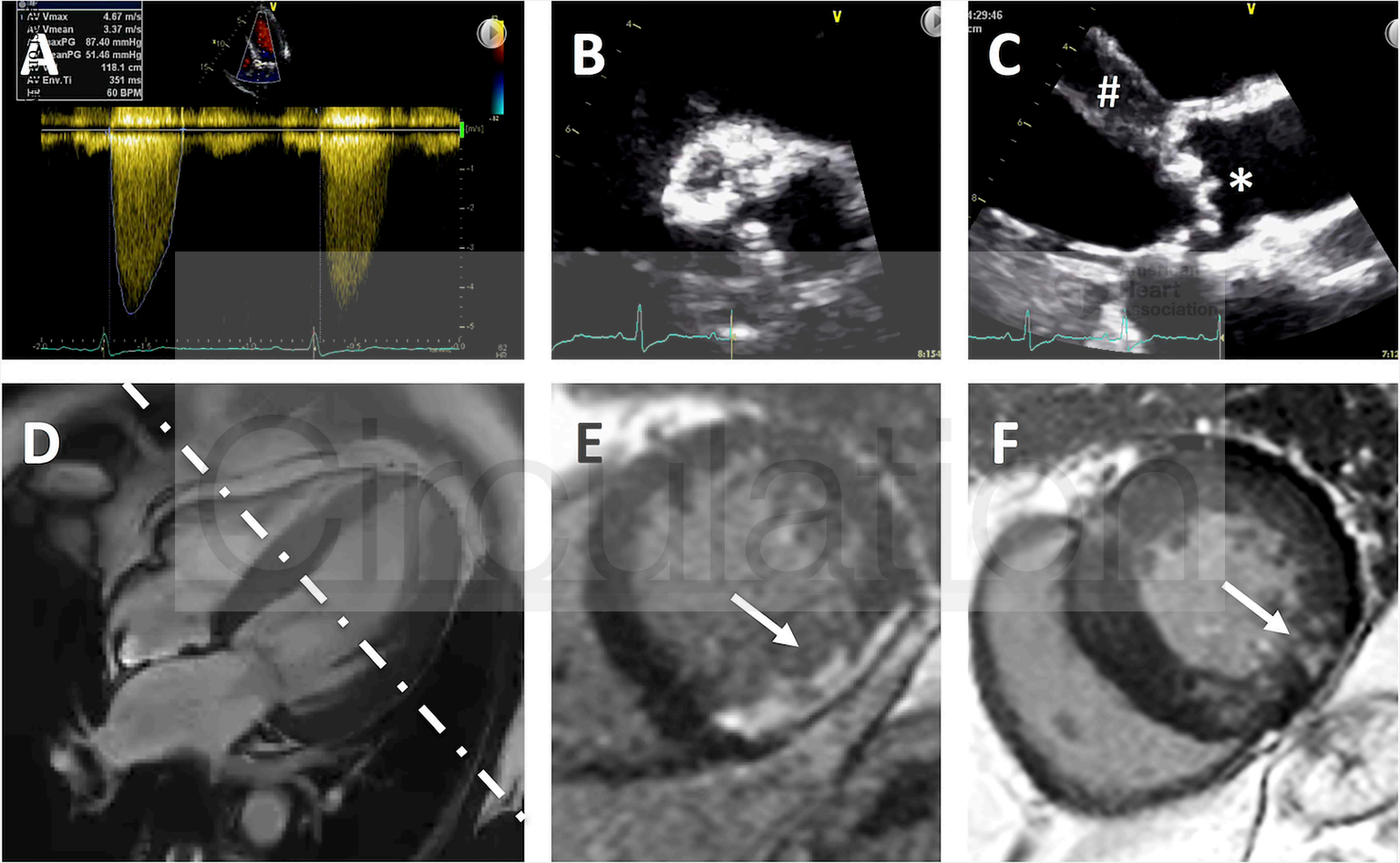
Assessment of aortic stenosis (AS) by transthoracic echocardiography (TTE, A-C) and cardiovascular magnetic resonance (D-F). A. Continuous Doppler trace across the aortic valve in the apical 5-chamber demonstrating hemodynamic parameters consistent with severe AS (peak velocity 4·67m/s, peak gradient of 87mmHg and mean gradient 51mmHg). B. Short axis TTE image of a severely calcified aortic valve. C. Parasternal long axis image demonstrating left ventricular hypertrophy (#) and a calcified aortic valve (*). D. Four chamber balanced SSFP cine image demonstrating left ventricular hypertrophy; the white dotted line demonstrates the axis of acquisition of the short axis (E+F). E. Late gadolinium enhancement (LGE) image in a mid-ventricular short axis showing transmural LGE of a full-thickness myocardial infarct (arrow). F. LGE image in a mid-ventricular short axis showing patchy non-ischemia LGE in the mid inferolateral segment (arrow) as well as more subtle LGE in the inferoseptum and right ventricular insertion points.

Figure 2. All-Cause and cardiovascular mortality in severe AS by LGE status.

Kaplan Meier survival plots showing all-cause (left) and cardiovascular (right) mortality in: all patients (A and B, n=674); patients treated with surgical aortic valve replacement (C and D, n=399); and patients treated with transcatheter aortic valve replacement (E and F, n=275), according to the presence or absence of late gadolinium enhancement (LGE) pre-operatively.

Figure 3. All-Cause mortality in severe AS by LGE pattern.

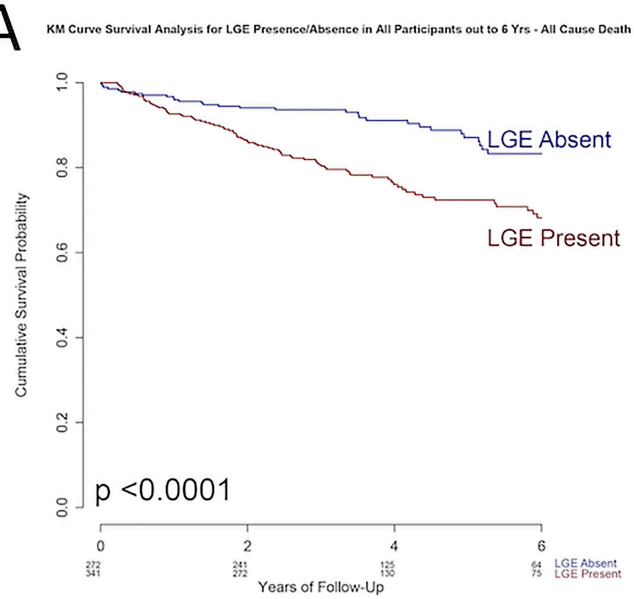
Kaplan Meier survival plot showing all-cause mortality in all patient with severe aortic stenosis (n=674) by pattern of late gadolinium enhancement (no LGE, infarct LGE, non-infarct LGE; both *p<0.001*). The plot is summarizing 6-year follow-up data.


A
AV Vmax 4.67 m/s
AV Vmean 3.37 m/s
MaxPG 87.40 mmHg
MeanPG 51.46 mmHg
118.1 cm
AV Env.Ti 351 ms
60 BPM
B
C
#
*
D
E
F

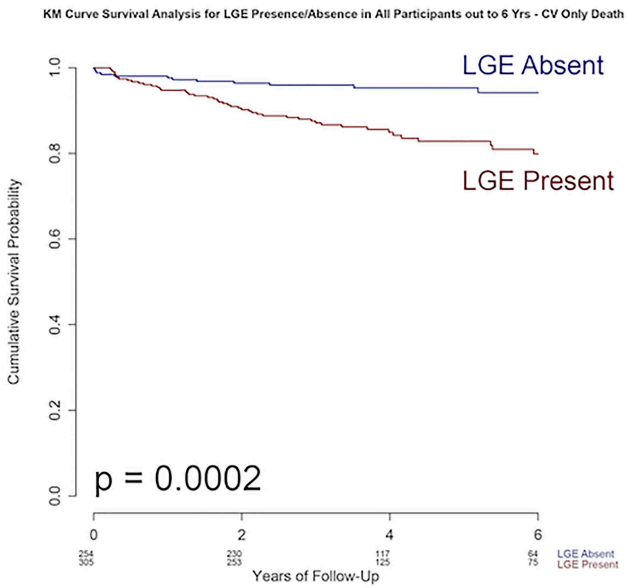
All-Cause Mortality

Cardiovascular Mortality

A

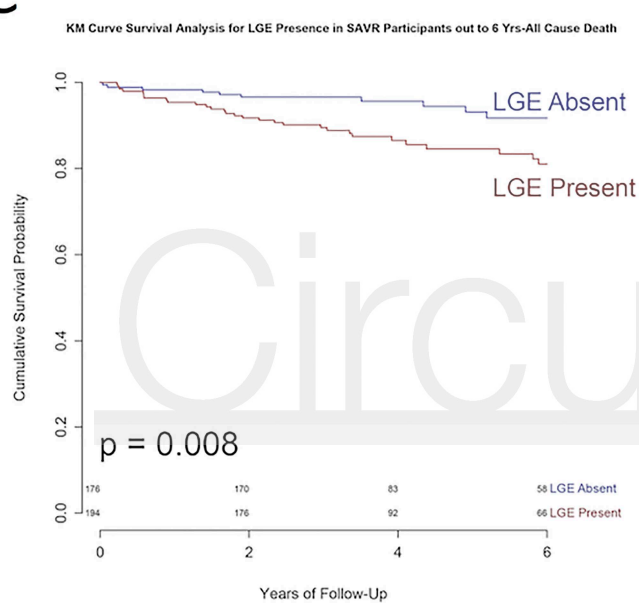


B



All

C



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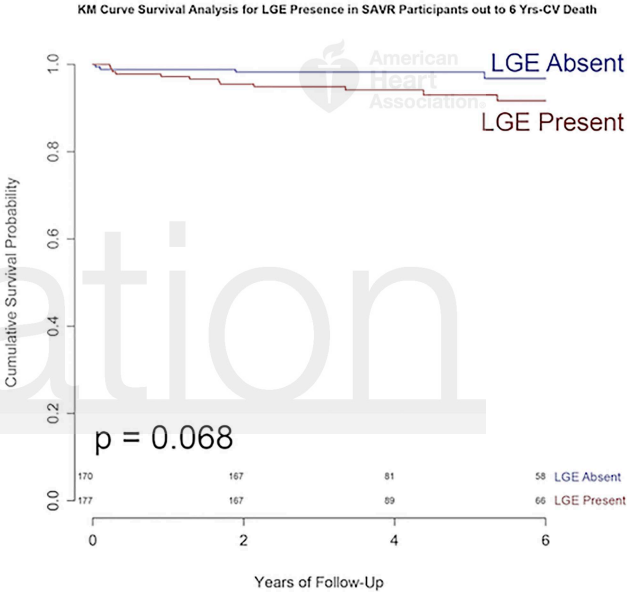
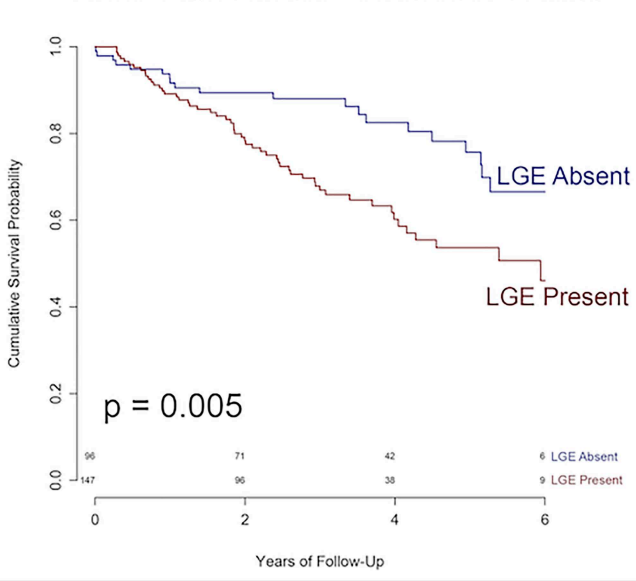
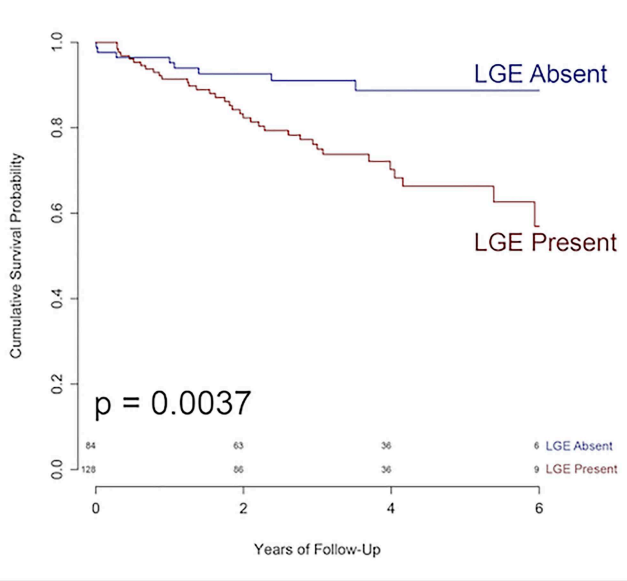


SAVR

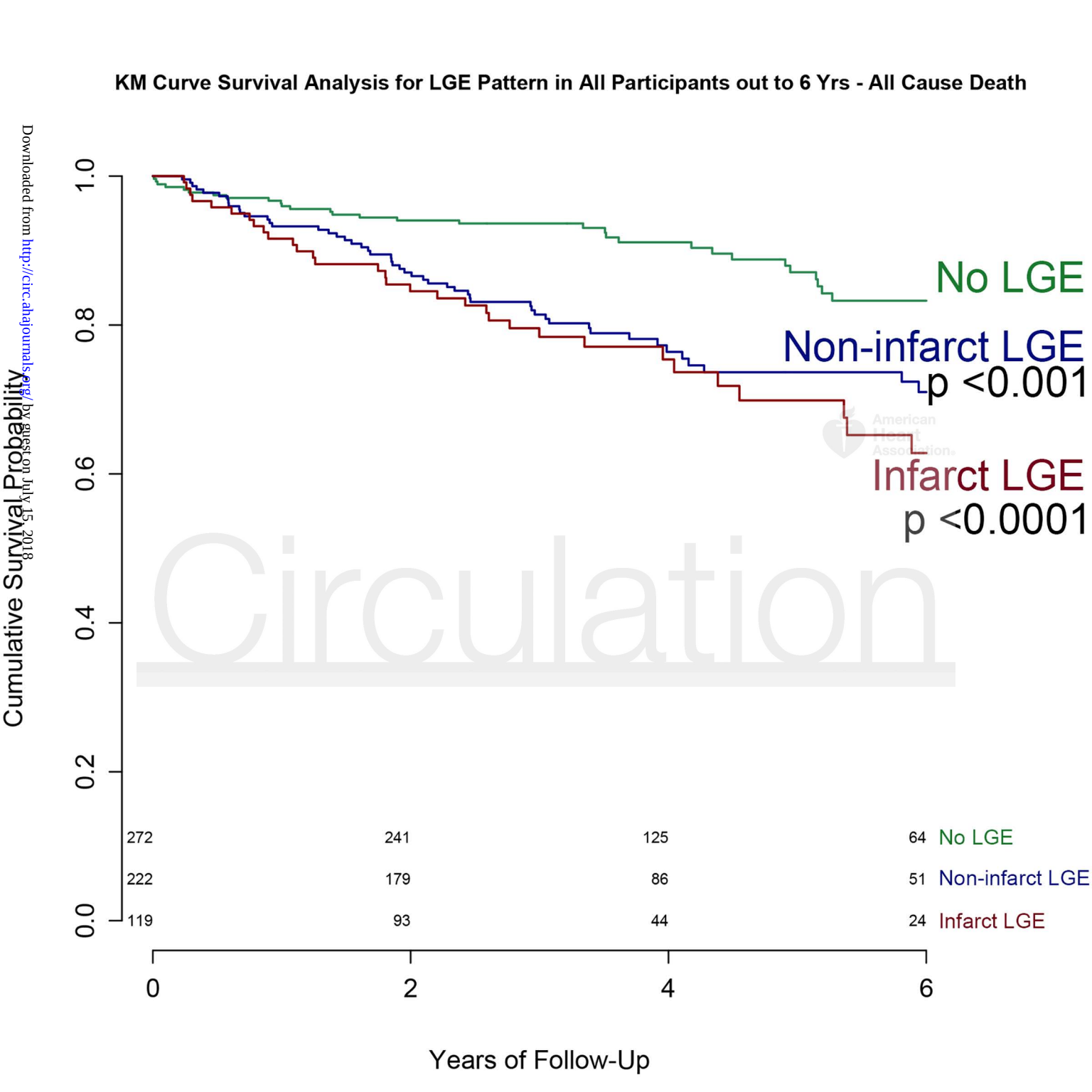
E



F



TAVR



Myocardial Scar and Mortality in Severe Aortic Stenosis: Data from the BSCMR Valve Consortium

Tarique A. Musa, Thomas A. Treibel, Vassiliou S. Vassiliou, Gabriella Captur, Anvesha Singh, Calvin Chin, Laura E. Dobson, Silvia Pica, Margaret Loudon, Tamir Malley, Marzia Rigolli, James R. J. Foley, Petra Bijsterveld, Graham R. Law, Marc Dweck, Saul G. Myerson, Gerry P. McCann, Sanjay K. Prasad, James C. Moon and John P. Greenwood

Circulation. published online July 12, 2018;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Myocardial Scar and Mortality in Severe Aortic Stenosis:

Data from the BSCMR Valve Consortium

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Overview:

1. **Figure S1: Study Diagram**

1. Figure S1: Study Diagram

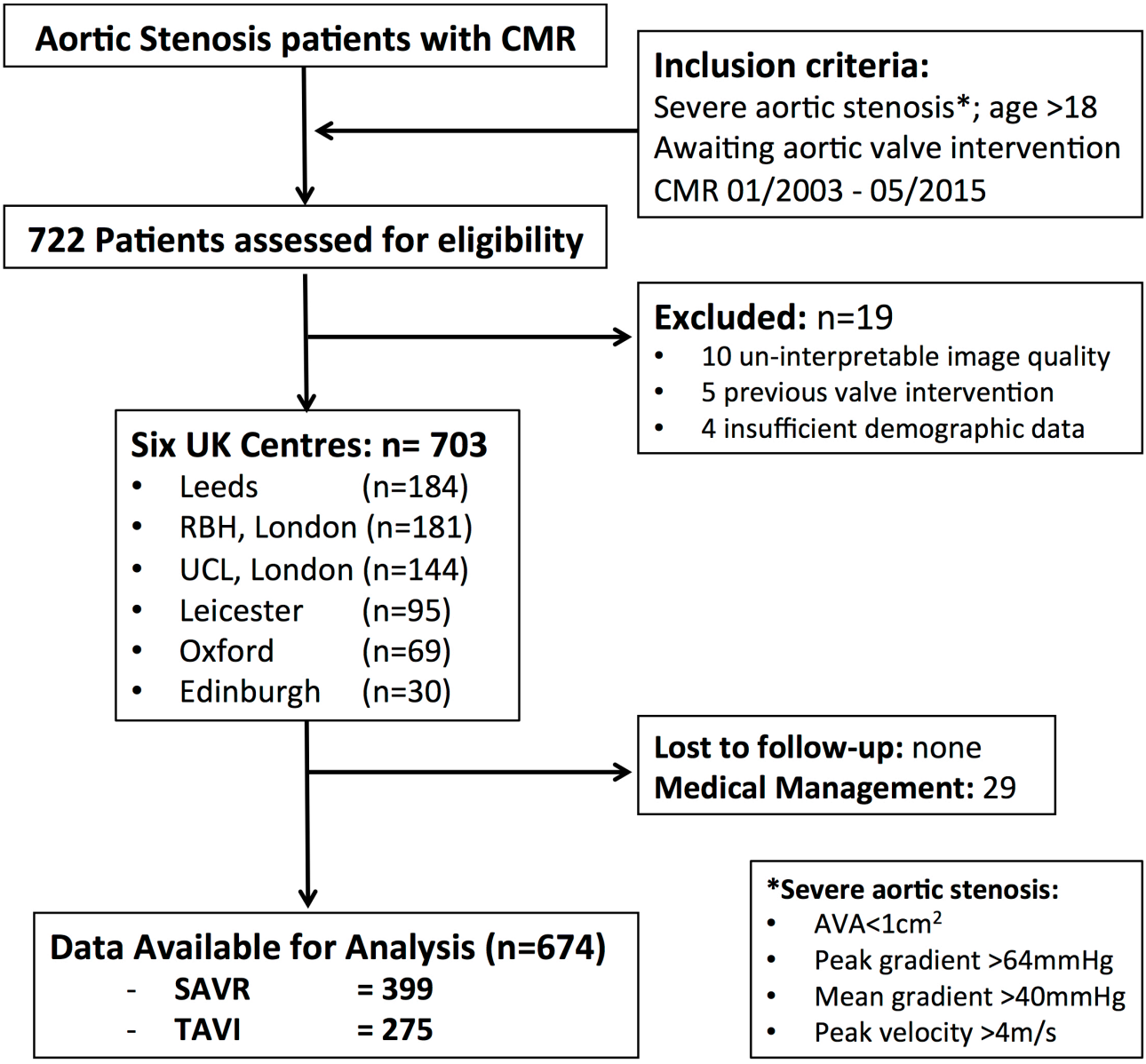
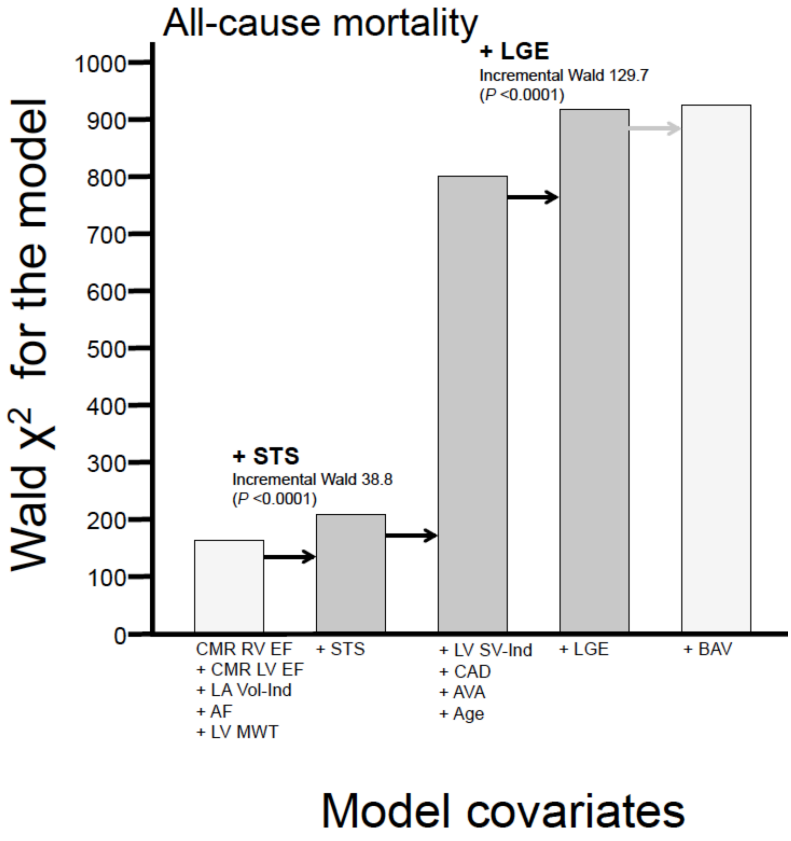


Figure S1: BSCMR AS700 Flow Diagram.
A longitudinal, observational outcome study in patients with severe AS referred to six UK cardiothoracic surgical centres and listed for valve intervention. Between January 2003 and May 2015, patients were prospectively recruited after evaluation by the multi-disciplinary heart team. Inclusion criteria were patients >18 years with severe AS (one of: aortic valve area [AVA]<1cm^2, peak pressure gradient >64mmHg, mean pressure gradient >40mmHg, peak velocity >4m/s) who had undergone CMR imaging for clinical or research purposes.
AVA, aortic valve area; CMR, cardiovascular magnetic resonance; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; RBH, Royal Brompton Hospital; UCL, University College London.

2. Figure S2: Incremental Risk Stratification

To demonstrate the sequence in which information becomes clinically available for risk stratification, the global Wald χ^2 are shown for separate Cox regression models predicting all-cause death, showing how the successive addition of volumetric indices, clinical variables, STS score and LGE significantly increase the global Wald χ^2 (probability values attributable to the addition of the new variable are also shown accounting for the variables already present in the model).



AF, atrial fibrillation; AVA, aortic valve area; BAV, bicuspid aortic valve; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; EF, ejection fraction; LGE, late gadolinium enhancement; LA, left atrium; LV, left ventricle; MWT, maximal wall thickness; STS, Society of Thoracic Surgery score; SV, stroke volume; Vol, volume.

3. Pre-specified Standard Operating Procedure for Data Analysis

Data analysis was pre-specified in a standard operating procedure document (SOP). This SOP ensured a consistent approach in respect of image analysis across the six sites. The analysis was performed in a distributed core-lab approach. All patients were uploaded as anonymised scans to a central repository. Each centre analysed a specific domain across the whole cohort (Figures in this section are not referred to in the main manuscript).

Standard Operating Procedure – BSCMR Valve Consortium

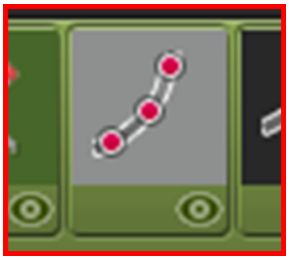
3.1 Circle Cardiovascular Imaging cvi42: Housekeeping

1) The same version of the CVI42 is utilised across the 6 sites (Version 5.1.2, Calgary, Canada). This, in particular, is important for those sites designated LV and RV chamber quantification. There are obvious differences in dashboard aesthetics and "smoothness" of contouring tools and it would be optimal for analysis to be performed on the same software.

2) To use a pre-specified zoom '%' of x2.0 or x2.7 for the workspace prior to contouring.

3) To use the pre-defined cvi windowing setting of 3 (although custom windowing should obviously be used if this setting is of suboptimal image quality)

4) Manual contouring of the LV and RV is performed using the bezier tool ('click-draw' icon displayed, see below).



5) To employ the following cvi42-specific SOP for standardising backend contour settings:

SubPixel Matrix size = 4X4
Signal Intensity SD = use subpixel weighted SD (and not biased SD)
Contour detection = check contour detection connect to view
Rounded SAX endocardial contour = leave inactive
Papillary muscle detection = check this
SAX chord generation = uncheck this

6) The contours drawn are saved locally

- "save workspace DICOM" via workspace option on task bar
- return to patient list view
- and choose "extended view" option at bottom left of screen
- select patient under study
- scroll down to end of sequence list and select the saved DICOM workspace
- right click on this and "export series"
- save in a designated folder on local drive

- upload contour workspace straight into the research participant's REDCap module using 'File Upload' option

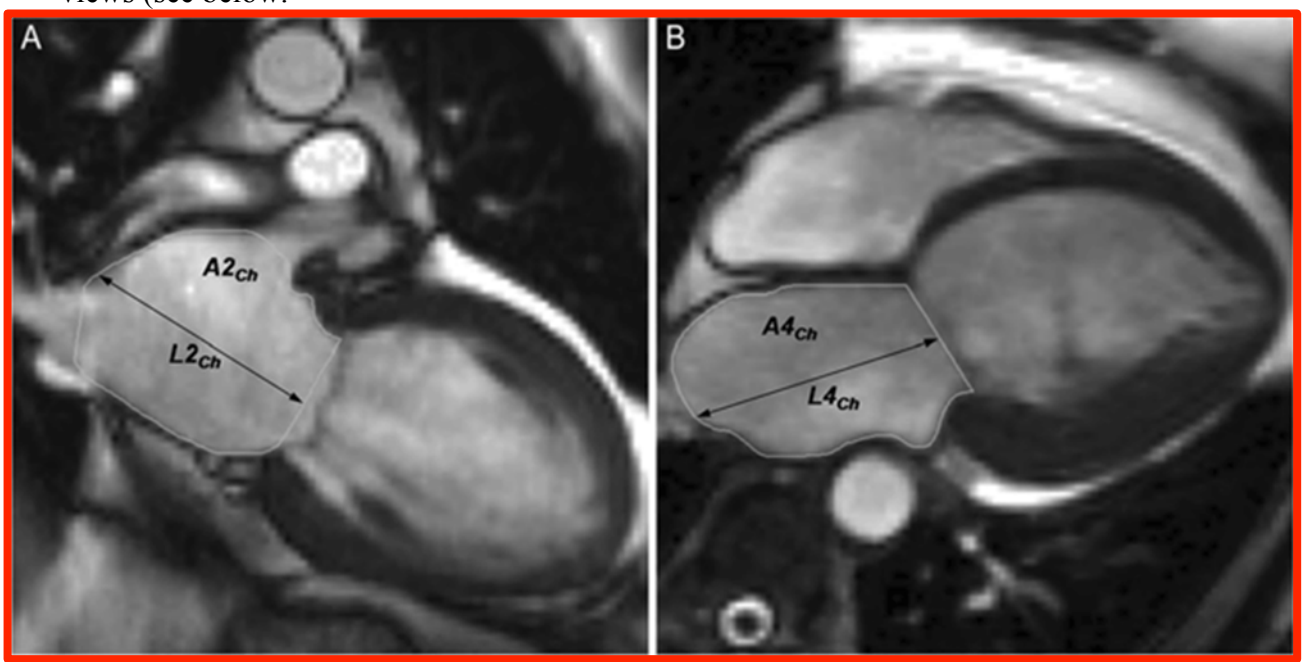
7) Similarly, that derived values (e.g. absolute LVEDV, LV mass etc) are manually entered into the CMR variables section of the BSCMR project in RedCAP under the patient being studied.

3.2 Left Atrial Volume Quantification

- Measurement of left atrial (LA) volume is by the biplane area–length method.
- Images are analysed in the viewer module of cvi42 with a dual panel display selected to permit synchronisation of HLA and VLA by phase.
- All measurements are taken from the two-chamber (A) and four-chamber (B) views at end-ventricular systole, ensuring maximal LA size.
- The atrial endocardial border is traced to determine LA area with exclusion of the pulmonary veins, LA appendage, and mitral valve recess.
- LA length is measured from the midpoint of the mitral annulus plane to the posterior aspect of the left atrium. Left atrial volume (LAV) was calculated using the formula:

$$LAV = 8(A2Ch)(A4Ch) / 3\pi L$$

- where A2Ch and A4Ch refer to the LA area in the two-chamber and four-chamber views, respectively, and L is the shorter of the two LA length measurements (L2Ch, L4Ch) from these views (see below.



(Adapted from Gulati et al. 2013. European Journal of Heart Failure; 15(6); 660-670).

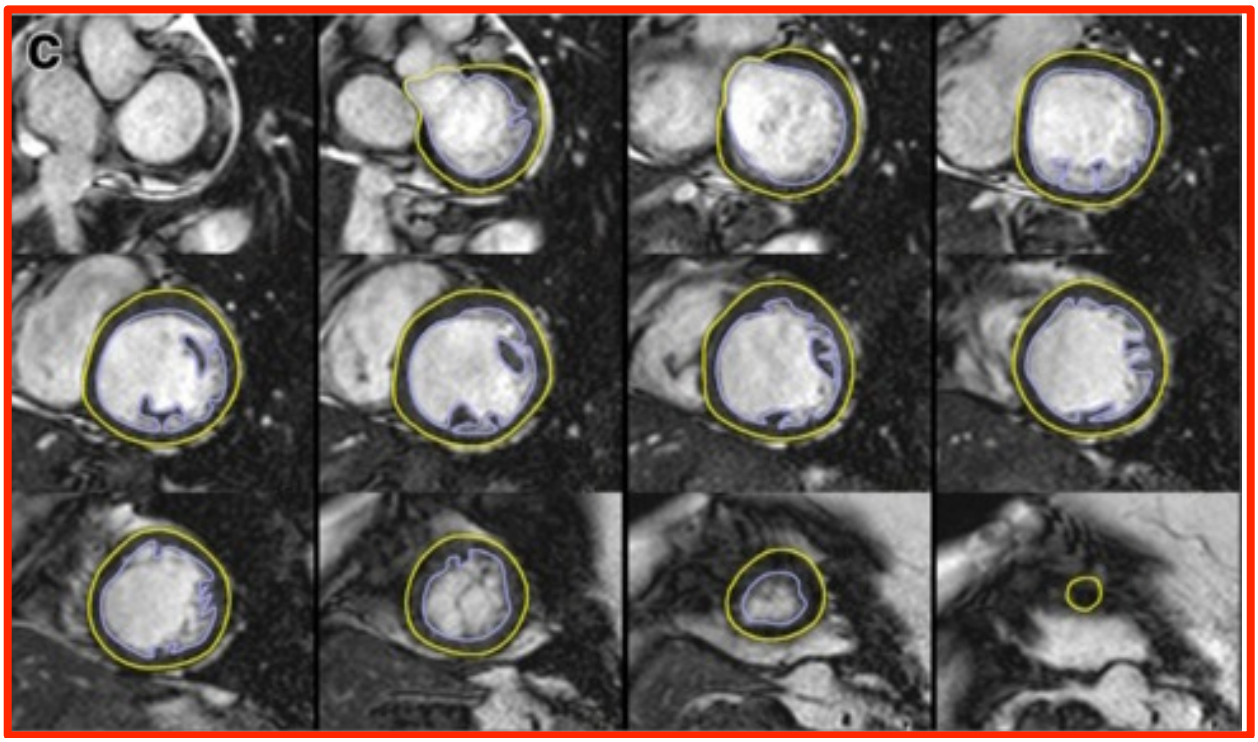
3.3 Left and Right Ventricular Volume and Mass Quantification

(adapted from Schulz-Menger et al. Journal of Cardiovascular Magnetic Resonance 2013, 15:35)

- For each study, LV and RV volumes and LV mass are to be contoured by the same one individual.
- If no intra- or extracardiac shunts are present, the RV and LV stroke volumes should be nearly equal (small differences are seen as a result of bronchial artery supply). Since the LV stroke volume is more reliably determined than the RV stroke volume, the LV data can be used to validate RV data.
- The dedicated LV short axis cine stack is to be contoured for both LV AND RV quantification.
- Manual contouring performed in cvi42 using the Bezier tool is the suggested method of analysis; the fully automated contour detection option is to be avoided.
- For the purposes of facilitating consistency of standards across different sites, a control sample of 5 cases will all be analysed by each of the three readers quantifying LV and RV parameters. These will then be surveyed by the PI to help provide feedback on technique and assist in answering any outstanding queries.

3.3.1 The Left Ventricle

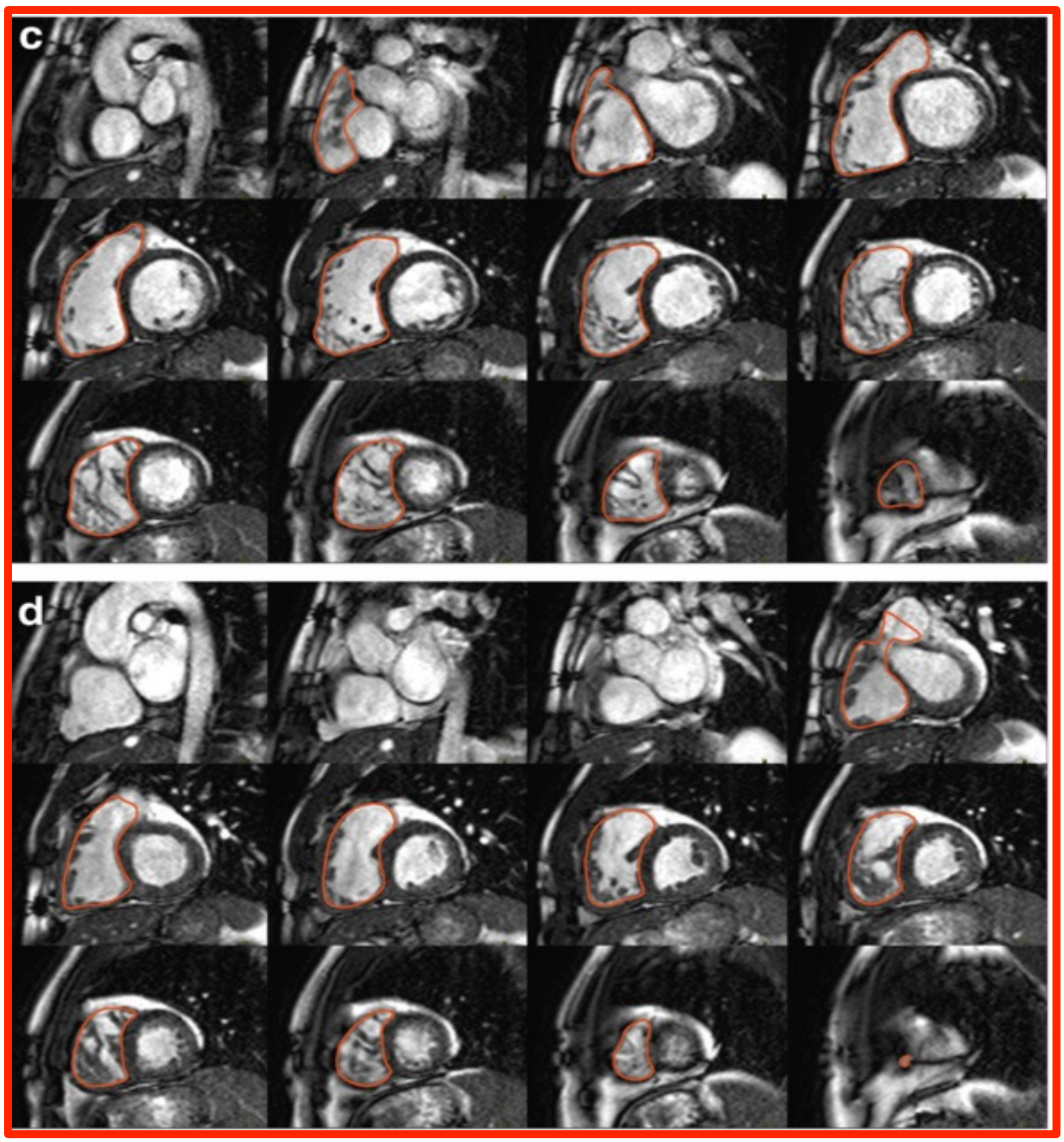
- The LV end-diastolic and end-systolic image should be chosen as the images with the largest and smallest LV blood volumes respectively. (For their identification, the full image stack should be evaluated)
- Deviations may occur and extra care should be taken in the setting of LV dyssynchrony or severe mitral regurgitation. Aortic valve closure defines end-systole.
- If a slice is uninterpretable (e.g. degraded by triggering/breathing artefact) it should be excluded from systolic and diastolic measurements of both the LV and RV.
- The LV outflow tract is included as part of the LV blood volume. When aortic valve cusps are identified on the basal slice(s) the contour is drawn to include the outflow tract to the level of the aortic valve cusps.
- Care must be taken with the one or two most basal slices. A slice that contains blood volume at end-diastole may include only left atrium (LA) without LV blood volume at end-systole. The LA can be identified when less than 50% of the blood volume is surrounded by myocardium and the blood volume cavity is seen to be expanding during systole.
- Papillary muscles are to be EXCLUDED from the LV cavity for the purpose of analysis and included within the LV mass (thus DO require specific delineation).
- Epicardial borders should be drawn on the middle of the chemical shift artifact line (when present).
- Absolute LV mass is derived from diastolic epicardial and endocardial delineation; systolic epicardial contours are NOT required.
- Maximal LV Wall Thickness is measured as the thickest portion of the interventricular septum in short axis at end diastole (mm)
- When the most basal slice contains only a small crescent of basal lateral myocardium and no discernible ventricular blood pool, an epicardial contour for the visible myocardium is included for LV mass only.
- Similarly, when the most apical slice contains only a circle of myocardium without cavitary blood pool, an epicardial contour without an endocardial contour should be drawn for LV mass calculations



Left ventricular (LV) chamber quantification. For LV chamber quantification, the endocardial (blue) and epicardial (yellow) contours are delineated in diastole in a stack of short axis slices that cover the whole left ventricle. c) illustrates the approach with EXclusion of the papillary muscles as part of the LV volume.

3.3.2 The Right Ventricle

- As for the LV, it may be necessary to review all image slices in the stack to define end-diastole and end-systole for the RV.
- Trabeculations of the RV are ignored and a smooth endocardial border is drawn to improve reader reproducibility (RV trabeculae and papillary muscles are typically included in RV volumes).
- Again, if no intra- or extracardiac shunts are present, the RV and LV stroke volumes should be nearly equal (small differences are seen as a result of bronchial artery supply).
- Since the LV stroke volume is more reliably determined than the RV stroke volume, the LV data can be used to validate RV data.
- The pulmonary valve may be visualized, and contours are included just up to, but not superior to this level.



Right ventricular (RV) chamber quantification. For RV volume quantification, the endocardial (red) contours are delineated in diastole (top) and systole (bottom) or short-axis (c and d) slices that cover the whole RV.

3.4 Aortic Valve haemodynamic assessment from quantification of VENC images

(adapted from Schulz-Menger et al. Journal of Cardiovascular Magnetic Resonance 2013, 15:35)

- Phase and magnitude images are analysed in the Flow module of cvi42 software.
- The dedicated aortic valve short axis cine (typically 8 slices) is viewed in the viewer module to determine the anatomic aortic valve orifice by 2D valve planimetry in peak systole when the opening of the aortic valve is widest. This is done by manually tracing the inner leaflet edges of the aortic valve cusps at the time of maximal opening; recording the average of three consecutive AVA measurements.
- Images are windowed to the appropriate brightness and contrast so that the borders of the ROI are sharp.

- Through-plane phase contrast images are examined to ensure the quality is sufficient and that the VENC chosen was appropriate.
- The borders of the vessel of interest are traced on each phase and magnitude image so that only the cavity of the vessel is included ensuring noise outside the vessel is not included
- Checks are made that this is performed correctly on the magnitude images (as always the phase images contain the encoded information)
- Where a number of phase contrast sequences have been acquired, the highest value for peak flow velocity and forward flow volumes should be recorded. Regurgitant fraction should be derived from non breath held images.

Pitfalls:
- On the phase images, the area of flow may be slightly larger than the area of the magnitude images.
- If aliased the sequence should be disregarded and another analysed.
- The use of software correction to analyse aliased images is to be avoided.
- In general, the area that exceeds the VENC in the ROI is in the centre of the vessel and not at the edges; if at the edges, it is usually (but not always) outside the vessel.

3.5 Late Gadolinium Enhancement Quantification

- All images are to be quantified using CVI 42.
- Manual epi and epdocardial quantification are performed from the dedicated LV volume short axis cine stack in end diastole in order to quantify LV mass (papillary muscles were excluded).
- The short axis LV stack acquired 10-15 minutes following Gadolinium (Doteram 0.2mmol/kg) contrast administration is used for the purposes of late gadolinium quantification.
- Each slice is visually inspected by 2 doctors experienced in MRI analysis for the presence or absence of gadolinium enhancement.
- Phase swap and other geometry images were used in order to assist in decision making where required.
- In only those slices deemed to have LGE present, epi and endocardial contours were manually drawn, with care take to exclude artefact, blood pool, fat and pericardium.
- The auto-identification tool was then applied and an area of normal remote myocardium defined alongside identification of areas with increased signal intensity.
- Any hyperintense regions felt to be related to artefact are manually excluded.
- The 2SD, 5SD and full width half max techniques are used to determined LGE mass.

NB: There was no significant difference in association of the different LGE quantification techniques. Previous reports showed that the FWHM technique was the most reproducible for infarct and non-infarct LGE (Flett et al. Circulation Cardiovascular Imaging 2011), thus we chose this *a priori* as the technique for our analysis.

4. Supplementary Tables:

4.1 TABLE S1: FOLLOW-UP AND MORTALITY

	All patients (n = 674)	All TAVR (n=275)	All SAVR (n=399)	P VALUE
Follow-up				
Follow-up duration post CMR date (days)	1515 ± 847	1190 ± 692	1740 ± 872	**<0.0001**
Mortality				
30-day mortality post intervention (%)	12 (1.8)	7 (2.6)	5 (1.3)	0.570
1-year mortality post intervention (%)	42 (6.2)	30 (10.9)	12 (3.0)	**<0.0001**
All – Cause Death, No. post CMR (%)	145 (21.5)	93 (33.8)	52 (13.0)	**<0.0001**
CV Death, No. post CMR (%)	70 (10.4)	51 (18.5)	19 (4.8)	**<0.0001**

4.2 TABLE S2: UNIVARIATE PARAMETERS – Surgical Aortic Valve Replacement.

Parameter	ALL SAVR (n=399)				ALL SAVR (n=399)			
	All Cause Mortality (n=52)				Cardiovascular Mortality (n=19)			
	HR	Z	P value	95% CI	HR	Z	P value	95% CI
Baseline Demographics								
Age	1.60	3.22	**0.001**	1.20 – 2.14	1.64	2.01	**0.044**	1.01 – 2.64
Male gender	0.99	-0.04	0.966	0.54 - 1.80	0.55	-1.27	0.205	0.22 – 1.38
BMI	1.02	0.76	0.447	0.97 - 1.08	1.07	1.40	0.163	0.97 – 1.17
Atrial Fibrillation	2.38	2.24	**0.025**	1.11 - 5.09	5.03	3.06	**0.002**	1.79 – 14.15
Diabetes Mellitus	1.61	1.59	0.112	0.89 - 2.91	2.22	1.67	0.095	0.87 – 5.64
Hypertension	1.73	1.81	0.070	0.96 - 3.12	1.10	0.20	0.846	0.44 – 2.74
Bicuspid AoV	0.51	-2.00	**0.046**	0.27 - 0.99	0.63	-0.90	0.369	0.23 – 1.74
Previous CAD	1.69	1.71	0.088	0.93 - 3.09	1.89	1.29	0.197	0.72 - 4.98
Previous PCI or CABG	0.71	-0.66	0.510	0.25 - 1.99	/	/	0.998	0 >inf
Previous MI	0.77	-0.50	0.616	0.28 - 2.15	1.23	0.20	0.842	1.16 – 9.25
Baseline Medications								
ACE inhibitor or ARB	1.41	1.22	0.223	0.81 - 2.46	1.61	1.03	0.304	0.65 - 3.95
β-blocker	0.85	-0.53	0.594	0.46 - 1.55	1.48	0.84	0.400	0.59 - 3.69
Aldosterone Antagonist	0.75	-0.40	0.692	0.17 - 3.19	1.04	0.04	0.971	0.13 - 8.28
Statin	1.47	1.20	0.231	0.78 - 2.75	2.32	1.49	0.138	0.76 – 7.06
STS score	1.15	1.74	0.083	0.98 - 1.34	1.19	1.57	0.115	0.96 – 1.48
Euroscore	1.03	0.57	0.569	0.93 - 1.13	1.04	0.44	0.662	0.88 – 1.22
Echo Data								
Mean AoV gradient	1.00	-0.12	0.908	0.98 - 1.02	0.99	-0.59	0.553	0.95 – 1.03
Peak AoV gradient	1.00	0.001	0.999	0.99 - 1.01	0.99	-0.41	0.682	0.97 – 1.02
AoV area	0.74	-0.45	0.654	0.20 - 2.79	0.26	-1.16	0.247	0.03 – 2.57
AoV area Indexed to BSA	0.66	-0.32	0.751	0.05 - 8.25	0.08	-1.11	0.269	0.001 - 6.81
Estimated PA pressure								
Moderate	1.42	0.70	0.487	0.53 - 3.78	1.94	0.81	0.417	0.39 – 9.63
Severe	5.27	2.67	**0.007**	1.55 - 17.88	12.8	3.06	**0.002**	2.50 – 65.90
CMR data								
LV end diastolic volume index	1.00	-0.28	0.780	0.99 - 1.01	1.00	-0.39	0.696	0.98 – 1.02
Indexed LV Stroke Volume	0.98	-1.48	0.140	0.96 - 1.01	0.96	-1.96	0.051	0.92 – 1.00
LV Ejection Fraction	0.99	-1.11	0.267	0.97 - 1.01	0.98	-1.27	0.205	0.95 – 1.01
Maximal LV wall thickness	0.99	-0.12	0.902	0.90 - 1.09	1.05	0.61	0.539	0.90 – 1.23
Indexed LV mass	1.00	-0.15	0.878	0.99 - 1.01	1.00	-0.15	0.883	0.98 – 1.02
RV end diastolic volume index	0.98	-2.20	**0.028**	0.96 - 1.00	0.96	-2.21	**0.027**	0.93 – 1.00
RV Ejection Fraction	1.00	-0.03	0.973	0.97 - 1.03	1.01	0.35	0.728	0.96 – 1.06
Indexed LA volume	1.01	1.38	0.167	1.00 - 1.03	1.02	1.92	0.056	1.00 – 1.04
CMR AoV regurgitant fraction	0.97	-1.84	0.066	0.93 - 1.00	0.96	-1.19	0.233	0.90 – 1.03
Valvulo-Arterial Impedance	1.04	0.23	0.817	0.77 - 1.40	0.98	-0.08	0.938	0.58 – 1.65
Late gadolinium enhacement (LGE)								
LGE presence / absence	2.05	2.25	**0.025**	1.09 - 3.84	2.42	1.68	0.093	0.86 – 6.80
LGE pattern								
Non-infarct pattern	2.11	2.22	**0.027**	1.08 - 4.06	2.03	1.24	0.214	0.66 – 6.21
Infarct pattern	1.90	1.45	0.147	0.80 - 4.54	3.52	1.99	**0.047**	1.02 – 12.15
LGE mass, per 1% increase	1.05	1.21	0.226	0.97 - 1.13	1.07	1.24	0.214	0.96 – 1.18

Abbreviations: SAVR, surgical aortic valve replacement; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; ARB, angiotensin receptor blocker; AVA, aortic valve area; PASP, pulmonary artery systolic pressure, LV, left ventricle; RV, right ventricle; LGE, late gadolinium enhancement.

3.3 TABLE S3: UNIVARIATE PARAMETERS – Transcatheter Aortic Valve Replacement.

Parameter	TAVR (n=275)				TAVR (n=275)			
	All Cause Mortality (n=93)				Cardiovascular Mortality (n=51)			
	HR	Z	P value	95% CI	HR	Z	P value	95% CI
Baseline Demographics								
Age*	1.43	2.55	**0.011**	1.09 – 1.89	1.65	2.54	**0.011**	1.12 – 2.42
Male Gender	0.94	-0.32	0.751	0.62 – 1.41	0.83	-0.65	0.513	0.48 – 1.44
BMI	0.97	-1.55	0.122	0.93 – 1.01	0.96	-1.59	0.113	0.91 – 1.01
Atrial Fibrillation	1.47	1.61	0.107	0.92 – 2.35	1.68	1.67	0.096	0.91 – 3.07
Diabetes Mellitus	1.07	0.27	0.785	0.67 – 1.70	1.53	1.46	0.144	0.86 – 2.73
Hypertension	1.20	0.87	0.386	0.80 – 1.81	1.34	1.04	0.301	0.77 – 2.32
Bicuspid AoV	0.30	-1.70	0.089	0.07 – 1.20	0.24	-1.43	0.154	0.03 – 1.72
Previous CAD	1.10	0.43	0.671	0.72 – 1.66	1.25	0.77	0.442	0.71 - 2.18
Previous PCI or CABG	1.01	0.04	0.968	0.65 - 1.58	1.19	0.59	0.558	0.67 – 2.11
Previous MI	1.10	0.33	0.745	0.61 – 1.99	0.89	-0.31	0.758	0.42 – 1.89
Baseline Medications								
ACE inhibitor or ARB	1.06	0.24	0.810	0.67 - 1.66	1.01	0.031	0.975	0.56 - 1.82
β-blocker	1.24	1.01	0.311	0.82 - 1.86	1.27	0.85	0.394	0.73 - 2.21
Aldosterone Antagonist	0.60	-1.11	0.266	0.24 - 1.48	0.99	-0.03	0.980	0.39 - 2.50
Statin	0.90	-0.49	0.621	0.59 - 1.38	0.90	-0.36	0.719	0.51 - 1.60
STS score	1.10	3.36	**<0.001**	1.04 – 1.16	1.12	3.37	**<0.001**	1.05 – 1.20
Euroscore	1.04	1.67	0.095	0.99 – 1.10	1.07	2.23	**0.026**	1.01 – 1.13
Echo Data								
Mean AoV gradient	1.00	0.00	1.000	0.98 – 1.01	0.99	-0.98	0.329	0.96 – 1.01
Peak AoV gradient	1.00	-0.53	0.595	0.99 – 1.01	0.99	-1.23	0.218	0.97 – 1.01
AoV area	0.99	-0.01	0.988	0.25 – 3.97	1.34	0.31	0.754	0.21 – 8.60
AoV area Indexed to BSA	1.94	0.52	0.600	0.16- 23.35	5.93	1.08	0.282	0.23 - 151.6
Estimated PA pressure								
Moderate	1.74	1.64	0.102	0.90 – 3.38	1.91	1.41	0.160	0.77 – 4.72
Severe	2.40	1.95	**0.052**	0.99 – 5.77	2.98	1.94	**0.053**	0.99 – 9.00
CMR data								
LV end diastolic volume index	1.00	-0.02	0.983	0.99 – 1.01	1.00	0.05	0.961	0.99 – 1.01
Indexed LV Stroke Volume	0.97	-3.52	**<0.001**	0.95 – 0.98	0.96	-2.97	**0.003**	0.94 – 0.99
LV Ejection Fraction	0.98	-3.03	**0.002**	0.97 – 0.99	0.97	-3.32	**<0.001**	0.95 – 0.99
Maximal LV wall thickness	0.97	-0.70	0.485	0.91 – 1.05	0.96	-0.76	0.446	0.87 – 1.06
Indexed LV mass	1.00	0.57	0.567	0.99 – 1.01	1.00	0.75	0.456	0.99 – 1.02
RV end diastolic volume index	1.00	-0.30	0.764	0.99 _ 1.01	1.00	0.17	0.867	0.99 – 1.02
RV Ejection Fraction	0.97	-3.29	**<0.001**	0.96 – 0.99	0.96	-3.52	**<0.001**	0.94 – 0.98
Indexed LA volume	1.00	0.95	0.341	1.00 – 1.01	1.01	1.23	0.218	1.00 – 1.02
CMR AoV regurgitant fraction	1.00	-0.37	0.709	0.98 – 1.02	0.98	-1.09	0.277	0.96 – 1.01
Valvulo-Arterial Impedance	1.08	0.74	0.457	0.89 – 1.31	1.11	0.77	0.440	0.85 – 1.45
Late gadolinium enhancement (LGE)								
LGE presence / absence	2.21	3.09	**0.002**	1.34 – 3.66	3.45	3.17	**0.001**	1.60 – 7.40
LGE pattern								
Non-infarct pattern	2.37	3.04	**0.002**	1.36 – 4.13	3.46	2.96	**0.003**	1.52 – 7.88
Infarct pattern	2.05	2.44	**0.015**	1.15 – 3.66	3.43	2.89	**0.004**	1.49 – 7.90
LGE mass, per 1% increase	1.07	3.36	**<0.001**	1.03 – 1.11	1.07	2.89	**0.004**	1.02 – 1.12

*Using age variable scaled by epochs of 10.

Abbreviations: TAVR, transcatheter aortic valve replacement; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; ARB, angiotensin receptor blocker; AVA, aortic valve area; PASP, pulmonary artery systolic pressure, LV, left ventricle; RV, right ventricle; LGE, late gadolinium enhancement.

3.4 TABLE S4: MULTI-VARIABLE MODEL – all cause mortality (SAVR Patients).

MULTIVARIABLE ANALYSIS TABLE FOR SAVR PATIENTS (LGE Present/Absent)

	ALL SAVR n=399					ALL SAVR n=399			
	ALL CAUSE MORTALITY (n = 52)					Cardiovascular MORTALITY (n = 19)			
Parameter	**HR**	**Z**	**P value**	**95% CI**	**Parameter**	**HR**	**Z**	**P value**	**95% CI**
Baseline Age*	1.53	2.48	**0.013**	1.09 - 2.14	Baseline Age	1.26	0.88	0.377	0.75 - 2.11
Atrial Fibrillation	2.79	2.36	**0.019**	1.19 - 6.57	Atrial Fibrillation	5.60	2.91	**0.004**	1.75 - 17.91
Indexed RV EDV	0.99	-0.79	0.428	0.97 - 1.01	Indexed RV EDV	0.98	-1.12	0.261	0.94 - 1.02
LGE Presence	2.14	2.25	**0.025**	1.10 - 4.15	LGE Presence	1.97	1.24	0.215	0.67 - 5.78

*Using age variable scaled by epochs of 10.

Abbreviations: EDV, end-diastolic volume; LGE, late gadolinium enhancement; RV, right ventricle; SAVR, surgical aortic valve replacement.

3.5 TABLE S5: MULTI-VARIABLE MODEL – All Cause Mortality (TAVR Patients).

MULTIVARIABLE ANALYSIS TABLE FOR TAVR PATIENTS (LGE Present/Absent)

	TAVR n=275					TAVR n=275			
	ALL CAUSE MORTALITY (n = 93)					Cardiovascular MORTALITY (n = 51)			
Parameter	**HR**	**Z**	**P value**	**95% CI**	**Parameter**	**HR**	**Z**	**P value**	**95% CI**
Baseline Age*	1.76	3.61	**<0.001**	1.29 - 2.38	Baseline Age	2.09	3.55	**<0.001**	1.39 - 3.15
CMR LV EF	1.00	-0.20	0.842	0.98 - 1.02	CMR LV EF	0.99	-0.78	0.437	0.97 - 1.02
CMR RV EF	0.98	-1.63	0.103	0.96 - 1.00	CMR RV EF	0.98	-1.49	0.136	0.95 - 1.01
LGE Presence	2.38	3.18	**0.001**	1.40 - 4.06	LGE Presence	3.47	3.09	**0.002**	1.58 - 7.65

*Using age variable scaled by epochs of 10.

Abbreviations: LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle; TAVR, transcatheter aortic valve replacement.

3.6 Table S6: MULTI-VARIABLE MODEL – ALL CAUSE MORTALITY: incorporating Pulmonary Artery Systolic Pressure (PASP).

	ALL PATIENTS (n=674)			
	ALL CAUSE MORTALITY (n= 145)			
Parameter	**HR**	**Z**	**P value**	**95% CI**
Age*	2.00	4.60	**<0.0001**	1.49 - 2.70
LGE Presence	1.92	2.20	**0.028**	1.07 - 3.43
LV ejection fraction	0.99	-0.75	0.451	0.97 - 1.01
Atrial fibrillation	1.31	0.74	0.457	0.65 - 2.65
CAD	0.81	-0.71	0.481	0.45 - 1.45
AVA (by echo)	1.00	0.001	0.999	0.31 - 3.24
LV maximal wall thickness	0.96	-0.84	0.398	0.88 - 1.05
RV ejection fraction	1.02	1.15	0.250	0.99 - 1.05
Estimated PA pressure				
Moderate	1.77	1.77	0.077	0.94 - 3.32
Severe	2.73	2.42	**0.016**	1.21 - 6.17

*Using age variable scaled by epochs of 10.
Abbreviations: AVA, aortic valve area; CAD, coronary artery disease; LGE, late gadolinium enhancement; LV, left ventricle.

3.7 Table S7: MULTI-VARIABLE MODEL – ALL CAUSE MORTALITY: incorporating coronary revascularization (previous CABG/PCI) instead of CAD.

	ALL PATIENTS (n=674)			
	ALL CAUSE MORTALITY (n= 145)			
Parameter	**HR**	**Z**	**P value**	**95% CI**
Age*	1.91	5,16	**<0.0001**	1.49 - 2.44
LGE Presence	2.30	3.16	**<0.002**	1.37 - 3.86
LV ejection fraction	0.99	-0.80	0.425	0.98 - 1.01
Atrial fibrillation	1.29	0.86	0.391	0.72 - 2.29
Prior PCI/CABG	1.17	0.63	0.529	0.71 - 1.92
AVA (by echo)	0.89	-0.24	0.814	0.33 - 2.41
LV maximal wall thickness	0.93	-1.83	0.068	0.86 - 1.01
RV ejection fraction	1.00	-0.21	0.833	0.98 - 1.02

*Using age variable scaled by epochs of 10.
Abbreviations: AVA, aortic valve area; CAD, coronary artery disease; LGE, late gadolinium enhancement; LV, left ventricle.

3.8 TABLE S8: MULTI-VARIABLE MODEL – percentage scar (All Patients).

MULTIVARIABLE ANALYSIS TABLE FOR ALL PATIENTS (LGE %)

	ALL PATIENTS (n=674)					ALL PATIENTS (n=674)			
	ALL CAUSE MORTALITY (n= 145)					Cardiovascular MORTALITY (n=70)			
Parameter	**HR**	**Z**	**P value**	**95% CI**	**Parameter**	**HR**	**Z**	**P value**	**95% CI**
Age*	2.06	5.56	**<0.0001**	1.60 – 2.66	Age*	2.04	4.56	**<0.0001**	1.05 - 1.13
Atrial Fibrillation	1.38	1.10	0.272	0.78 – 2.42	Male Gender	0.53	-2.42	**0.016**	0.24 - 0.76
Previous CAD	1.20	0.81	0.419	0.77 - 1.89	Atrial Fibrillation	1.57	1.52	0.129	0.46 - 1.94
CMR LV EF	0.99	-0.72	0.474	0.98 - 1.01	Previous CAD	1.48	1.47	0.141	0.86 - 2.83
Echo AVA	1.06	0.11	0.910	0.39 – 2.88	CMR LV EF	0.98	-2.86	0.004	0.96 - 1.00
CMR RV EF	1.00	-0.43	0.670	0.97 - 1.02	LGE mass, per 1% increase	1.08	3.20	**0.001**	1.01 - 1.17
CMR LV maximal wall thickness	0.94	-1.58	0.113	0.87 – 1.01					
LGE mass, per 1% increase	1.11	3.80	**<0.001**	1.05 - 1.17					

*Using age variable scaled by epochs of 10.
Abbreviations: AVA, aortic valve area; CAD, coronary artery disease; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle.

3.9 Table S9: MULTI-VARIABLE MODEL – ALL CAUSE MORTALITY: excluding the 12 patients with 30-day post intervention mortality.

	ALL PATIENTS (n=662)			
	ALL CAUSE MORTALITY (n= 133)			
Parameter	**HR**	**Z**	**P value**	**95% CI**
Age*	1.95	5.13	**<0.0001**	1.51 - 2.57
LGE Presence	2.46	3.22	**0.013**	1.42 - 4.27
LV ejection fraction	0.99	-0.88	0.378	0.98 - 1.01
Atrial fibrillation	1.19	0.56	0.573	0.65 - 2.20
CAD	1.15	0.59	0.553	0.72 - 1.86
AVA (by echo)	0.81	-0.39	0.699	0.28 - 2.33
LV maximal wall thickness	0.94	-1.56	0.119	0.86 - 1.02
RV ejection fraction	1.00	-0.27	0.788	0.97 - 1.02

*Using age variable scaled by epochs of 10.
Abbreviations: AVA, aortic valve area; CAD, coronary artery disease; LGE, late gadolinium enhancement; LV, left ventricle.

3.10 Table S10: MULTI-VARIABLE MODEL – ALL CAUSE MORTALITY: changing index date to time of intervention.

	ALL PATIENTS (n=662)			
	ALL CAUSE MORTALITY (n= 133)			
Parameter	**HR**	**Z**	**P value**	**95% CI**
Age*	1.93	5.28	**<0.0001**	1.51 - 2.47
LGE Presence	2.16	2.95	**0.003**	1.30 - 3.61
LV ejection fraction	0.99	-0.92	0.358	0.98 - 1.01
Atrial fibrillation	1.33	0.97	0.330	0.75 - 2.36
CAD	1.19	0.74	0.459	0.74 - 1.87
AVA (by echo)	1.01	0.02	0.988	0.37 - 2.72
LV maximal wall thickness	0.93	-1.90	0.058	0.86 - 1.01
RV ejection fraction	1.00	0.01	0.989	0.98 - 1.02

*Using age variable scaled by epochs of 10.
Abbreviations: AVA, aortic valve area; CAD, coronary artery disease; LGE, late gadolinium enhancement; LV, left ventricle.